REMARKS

Claims 2, 3, 5-7, 9-11, 14-17, 19, and 22-23 are pending in the present application. By this Amendment, Applicants have amended claim 10 to correct a typographical error. No new matter has been added.

The May 1, 2009 Office Action

Previous Rejections Withdrawn

The Office Action stated that Applicants' arguments filed April 9, 2009 were persuasive and obviated all grounds of all rejections of record. Accordingly all previous rejections have been withdrawn.

In response, Applicants acknowledge and appreciate the withdrawal of the previous rejections.

Rejections under 35 U.S.C. §112, second paragraph

Claim 10 was rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite The Office Action noted that the claim ends with the phrase "nerve growth stimulate" when -- nerve growth stimulant – apparently was intended.

In response, Applicants have amended claim 10 in accordance with the Office Action's suggestion. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §103

Claims 2-3, 5-6, 9-11, 19, 14-16, 22-30, and 32-33 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Chamberlain et al. (reference 19 of IDS filed 3/10/04, "Chamberlain") in view of Geistlich et al. (reference 5 of IDS filed 3/10/04, US 5,837,278, "'278 patent") and further in view of Geistlich et al. (reference 1 of IDS filed 3/10/04, US 6,221,109, "'109 patent").

According to the Office Action, Chamberlain teaches collagen tubes for nerve regeneration that can be filled with a type I collagen/chondroitin-6-sulfate material (collagen and a glycosaminoglycan copolymer known as collagen-GAG (CG) copolymer) that acts as a nerve growth stimulant. The Office Action further stated that said tube is 20mm long with an internal diameter of 1.5mm (directing attention to the abstract, pages 1394-1395, and Figure 1). According to the Office Action, the collagen fiber filling material is longitudinally oriented with respect to the tube (page 1395) and laminin can be a promoter of nerve regeneration inside the tube (page 1394). The Office Action stated that Chamberlain discloses methods of placing nerves inside the tubes for regeneration (abstract and pages 1395-1396). (The Office Action noted that Myron Spector is a co-author of the Chamberlain et al. reference, and is also a co-inventor of the instant Application).

The Office Action acknowledged that Chamberlain does not teach a tube formed from a single sheet of collagen prepared from peritoneal membrane that has an outer smooth barrier surface and a soft fibrous surface opposite the smooth barrier surface. The Office Action asserted that the '278 patent discloses a single sheet of a resorbable sidewall material consisting essentially of a single layer collagen sheet material having a compact, smooth outer barrier

surface so as to inhibit cell adhesion thereon and act as a barrier to prevent passage of cells therethrough, and this sheet material further has a fibrous inner surface opposite the smooth barrier surface (column 1, line 51 to column 2, line 6) derived from collagen membrane peritoneal tissue (column 2, lines 52-60). The Office Action noted that this single layer collagen sheet material is identified as Bio-Gide® by the instant specification (page 3, paragraphs 0017 and 0018), and is the same material disclosed in the '278 patent. The Office Action has taken the position that Bio-Gide® inherently meets all the claim limitations of claims 2-3, 11, 14-15, 23-28, and 33. (The Office Action noted that Peter Geistlich is a co-inventor of the '278 patent and is a co-inventor of the instant Application). The Office Action acknowledged that the '278 patent does not disclose that Bio-Gide® is suitable for use with nerve tissue. The Office Action further stated that the '109 patent (second Geistlich et al. reference) teaches that Bio-Gide® can be wrapped around the spinal cord and dura sheath in order to protect both from injury during spinal surgeries and also to protect the spinal area from ingrowth of connective tissue and undesired cells which might interfere with proper healing. (The Office Action directed attention to column 1, lines 9-1 8 and column 1, line 54 to column 2, line 9 and to Figures 1 and 3).

On the basis of the above, the Office Action has concluded that it would have been obvious to one of ordinary skill in the art at the time of the invention to make and use the collagen tubes of Chamberlain with the Bio-Gide® of the prior art patents because, in the opinion expressed in the Office Action, while Chamberlain teaches that collagen tubes have multiple advantages over silicone tubes, "the required characteristics of a nerve guide remain to be fully delineated" (citing page 1401). The Office Action further stated that while porous collagen tubes permit diffusion of nutrients and growth-promoting factors from the external environment to the injured nerves in order to promote nerve regeneration (an observation the

Office Action indicated is supported by two studies according to Chamberlain), if the tube is too porous, important wound-derived neurotrophic factors may be allowed to exit the injury site prematurely through the tube. The Office Action stated that Chamberlain reports that his own study has shown that the most favorable results were obtained with a non-porous collagen tube filled with a CG copolymer because said tube facilitated the retention of the endogenous neurotrophic factors in the nerve injury gap site while allowing for the infiltration of smaller molecular weight nutrients through the tube. The Office Action asserted that Chamberlain concludes "additional experimentation with porous and non-porous collagen tubes that differ in permeability may be used to address this issue" (page 1402), which, in the opinion expressed in the Office Action, is an explicit direct suggestion by the primary reference to substitute the finite group of other known collagen tubes for the known and motivating purpose of improving the therapeutic results. The Office Action asserted that a clear nexus thus forms between the '109 patent which teaches Bio-Gide® collagen membranes formed into a tube around nerve tissue (spinal cord) (Figure 1 of the '109 patent) with the smooth barrier face facing the exterior to protect the surgical site from ingrowth of unwanted cells (column 3, lines 5-10) while the fibrous face opposite the smooth face faces inward, allowing cell growth thereon (column 2, lines 1-4 and Figure 3), and the Chamberlain reference which discloses that "in the tubulization method of treating nerve gaps, tubes can enhance regeneration by serving to (1) contain matrices that have been found to enhance the regenerative process, perhaps by providing a scaffold for 'contact guidance' . . . (2) prevent ingrowth of adjacent tissue into the gap, and thereby prevent fibrocollagenous scar formation in the gap" (directing attention to pages 1399-1400). The Office Action asserted that both the '109 patent and Chamberlain share a nexus to combine Bio-Gide® with the nerve regeneration methods of Chamberlain because, in the opinion expressed in the

Office Action, Bio-Gide® has an interior surface that allows cell growth thereon ('109 patent) which the Office Action asserted is very similar to providing a scaffold for 'contact guidance' (Chamberlain). The Office Action further stated that Bio-Gide® has an exterior surface preventing ingrowth of unwanted cells which, according to the Office Action, is exactly equivalent to preventing ingrowth of tissue that would form scars in the nerve gap and inhibit nerve regeneration (directing attention to Chamberlain). The Office Action asserted that the '278 patent makes the connection between Chamberlain's suggestion to try other collagen tube materials in order to make and use a better nerve regeneration tube with the Bio-Gide® of the '109 patent even stronger because, in the opinion expressed in the Office Action, the '278 patent reiterates the advantages of Bio-Gide® in relation to its desired property of excluding unwanted cells and simultaneously providing a fibrous surface that improves the ability of wanted cells to grow. (The Office Action directed attention to claims 1 and 18 of the '278 patent).

The Office Action further asserted that the '278 patent also teaches the advantages of making and using Bio-Gide® with chondroitin sulfate (directing attention to claim 11) and glycosaminoglycan (directing attention to claims 9, 12, and 24), which, according to the Office action also is disclosed by Chamberlain for improving his collagen tubes (the Office Action citing pages 1395 and 1402). In the opinion expressed in the Office Action, given the combined teachings of the three references, it would have been *prima facie* obvious to substitute the collagen of the nerve regeneration tubes of Chamberlain with the Bio-Gide® collagen of the patents because of the known advantageous properties of the two different surfaces of Bio-Gide® in order to make and use an improved collagen nerve regeneration tube, which the Office Action asserted is explicitly and directly suggested by Chamberlain. The Office Action finally concluded that because, in the opinion expressed in the Office Action,

all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention because the nexus between all the references makes the substitution of a known similar product (Bio-Gide® collagen for collagen type I) from a finite list of known collagens for a known similar purpose (nerve tissue healing) in order to produce a known similar result (improved tissue healing by improved interior cell growth while excluding unwanted exterior cells) with a reasonable expectation of success is also *prima facie* obvious. See *KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727(US. 2007).*"

In response, Applicants respectfully traverse the rejection. The present claims are directed to a nerve regeneration tube for reconnecting nerve ends, a method for producing such a tube, and a method of reconnecting nerve ends utilizing such a tube. The tube is resorbable and has a resorbable sidewall formed with collagen sheet material having a compact smooth outer barrier surface, and a soft fibrous inner surface opposite the smooth barrier surface. The tube has a compact smooth outer barrier surface formed with the compact smooth outer barrier surface of the collagen sheet material so as to inhibit cell adhesion thereon and to act as a barrier to prevent passage of cells therethrough. The tube further has a soft fibrous inner surface for promoting nerve growth, the soft fibrous inner surface of the tube being formed with the soft fibrous inner surface of the collagen sheet material. The tube has an inner diameter of about 0.5 – 5 mm, and has opposite tube ends, within which tube ends, during use, are nerve ends for reconnection of the nerve ends, wherein the nerve regeneration tube avoids formation of scar tissue which impairs nerve healing. Thus, the present claims refer to a <u>soft fibrous inner surface opposite the compact smooth outer barrier surface to facilitate nerve regeneration</u>.

First, Applicants note the Office Action's specific acknowledgment that "Chamberlain does not teach a tube formed from a single sheet of collagen prepared from peritoneal membrane

that has an outer smooth barrier surface *and a soft fibrous surface opposite the smooth barrier surface*." (Emphasis added). This is a significant fact in that, as Applicants have noted before, the present invention has unexpectedly advantageous properties over tubes not having this feature, including, specifically, the type of tube referred to in the cited Chamberlain reference. In that regard, Applicants refer to the Declaration of Dr. Myron Spector and accompanying data and remarks first submitted in the papers filed October 22, 2007 and discussed subsequently in the papers filed May 21, 2008 and April 9, 2009. Applicants note that the Declaration does indeed provide evidence of unexpected results over the presently cited prior art for reasons similar to those which were found persuasive in overcoming the rejections over previously cited art. As noted earlier, Dr. Spector is one of the inventors in the above-referenced application and is a renowned expert in the field. Dr. Spector has been a Professor of Orthopedic Surgery at Harvard Medical School since 1993, and has conducted research on nerve regeneration tubes for over a decade.

As indicated in Dr. Spector's Declaration, the *surface configuration of tubes defined by the present claims provides such tubes with unexpected properties which could not have been predicted based upon the prior art.* As noted previously and above, Dr. Spector has been researching nerve regeneration tubes for more than a decade. During earlier research that Dr. Spector participated in, comparisons were made between collagen nerve regeneration tubes and silicone nerve regeneration tubes, see, e.g., the papers attached to Dr. Spector's declaration as Exhibit B, Chamberlain et al., Histological response to a fully degradable collagen device implanted in a gap in a rat sciatic nerve, Tissue Engineering, 3,4:353-362, 1997, and Exhibit C, Chamberlain et al., Connective tissue response to tubular implants for peripheral nerve regeneration: the role of myofibroblasts, J. Comp. Neurol. 417:415-430, 2000. The collagen

tubes that were used in these earlier studies were obtained from Integra Life Sciences (Integra), Plainsboro, NJ, and are fabricated by freeze-drying Type I microfibrillar collagen from bovine tendon. The presently cited Chamberlain paper also refers to the Integra bovine tendon collagen type tubes (see, e.g., page 1395, column 1). The Integra collagen tubes are formed by collagen slurry injection over glass rods, and do not have a soft fibrous inner surface (as the Office Action has acknowledged), a fact that Dr. Spector did not consider relevant at the time. In the earlier studies reported in Exhibits B and C, the Integra tubes were compared to silicone nerve regeneration tubes using a severed sciatic nerve rat model. Both studies show that the silicone tubes resulted in substantially greater build-up of fibrous scar tissue within the tubes, as compared to the Integra collagen tubes, with the Exhibit C study indicating that the silicone tubes resulted in formation of a fibrous capsule 10 times thicker than in the Integra collagen tubes. The problem with such fibrous build-up is that this fibrous tissue contains contractile fibroblasts (myofibroblasts) which cause the contracture of the fibrous layer. The contracting fibrous cuff interferes with the elongation of axons through the tube, and thus interferes with nerve regeneration. Although Dr. Spector did not recognize the significance at the time, the silicone tubes have a smoother inner surface than the Integra collagen tubes. Instead, at the time, Dr. Spector and his co-workers noted in the Exhibit C report that: "The differences in connective tissue response between collagen and silicone tubes could have been due to their known differences in chemical composition, permeability, or degradability." Importantly, Dr. Spector's subsequent research and analysis indicates the thickness of the fibrous scar which forms along the inner surface of the tube is related to the topography of the surface, with smoother surfaces favoring the formation of a thicker scar layer with a great number of contractile cells.

As also noted in Dr. Spector's Declaration, the Geistlich '278 patent discloses a resorbable collagen membrane which is surgically inserted around the periphery of a wound cavity to facilitate, e.g., bone regeneration. There is no reference to nerve regeneration or any use in connection with nerves, nor is there any reference to formation of tubes for any purpose. In view of this reference, when combined with the other applied references, persons of ordinary skill in the art could not have predicted the unexpected results which have been achieved with the present invention, as outlined below.

In that regard, attached to Dr. Spector's Declaration as Exhibit D was a summary of a study that Dr. Spector was involved in, and which was presented at the 2007 Society for Biomaterials meeting. The Exhibit D study compares results achieved in five groups of animals (Groups I-V) in a rat spinal cord model for nerve regeneration. The study included testing of the collagen tubes (Groups III and IV) which Dr. Spector and his co-workers fabricated by freeze drying Type I microfibrillar collagen from bovine tendon from Integra, after slurry injection of the collagen over a glass rod mandrel. As noted, these Integra tubes do not have a soft fibrous inner surface.

As indicated in Dr. Spector's Declaration, the Exhibit D study included testing of BioGide® collagen membrane (Group V) from Geistlich Biomaterials, Wolhusen, Switzerland. This BioGide® collagen membrane material corresponds exactly to the BioGide® collagen sheet material exemplified in the present application and usable in accordance with the present claims. The BioGide® membrane sheet material utilized in Group V of the Exhibit D study has a compact smooth outer barrier surface and a soft fibrous inner surface. In Group V of the Exhibit D study, the tube was formed by wrapping BioGide® membrane sheet material around stump ends of severed spinal nerves, so as to form a nerve regeneration tube as set forth in the present

claims, with the soft fibrous surface oriented inwardly toward the severed nerve tissue to form the inner surface of the tube.

As indicated in Dr. Spector's Declaration, in the Exhibit D study, the Group V animals with tubes formed of Geistlich BioGide® membrane material having a smooth outer surface and a soft fibrous inner surface, unpredictably had the highest number of axons in the center of the nerve defect, see, Figure 1 in Exhibit D.

As indicated in Dr. Spector's Declaration, in the Exhibit D study, the only difference between the Group V animals and the Group IV animals was the structure of the tubular material surrounding the severed nerve tissue. The "dorsal barrier" mentioned in the Exhibit D study refers to a collagen membrane draped over the implant site to assist in preventing overlying tissue (e.g., muscle) from collapsing into the nerve defect.

As indicated in Dr. Spector's Declaration, taking into consideration the differences in the tube structure alone, between the Group V and Group IV animals, persons of ordinary skill in the art could not have predicted that the presently claimed invention, utilizing the collagen membrane material of Geistlich et al. U.S. Patent No. 5,837,278 (Group V), could result in the unexpectedly highest number of center nerve axons among the test animals, as compared to collagen tubes without a soft fibrous inner surface (the Group IV tubes, i.e., the Integra tubes, the very type referred to in the presently cited Chamberlain reference).

Moreover, as indicated in Dr. Spector's Declaration, with reference to Exhibit E attached thereto, Fig. 1 thereof shows a cross-section through the BioGide® collagen membrane material with the compact smooth barrier side at the top, and the soft fibrous side at the bottom. As shown in Fig. 2 of Exhibit E, entubulation of a gap in a rat nerve (spinal cord) with BioGide® demonstrated the absence of a thick fibrous scar on the inner surface of the tube, and

demonstrated the ingrowth of cells and tissue into the soft fibrous surface. Based on the prior art, persons of ordinary skill in the art could not have predicted the absence of a thick fibrous scar on the inner surface of a tube according to the present invention, in conjunction with ingrowth of cells and tissues into the soft fibrous inner surface of the tube.

The '109 patent is directed to use of collagen membranes to protect the spine after vertebral surgery. This is on an astronomically larger scale than the present invention, and is totally unrelated to the present invention. As set forth in the present application, the nerve regeneration tubes of the present invention are for reconnecting tiny nerves by inserting nerve ends in opposite ends of the inventive regeneration tubes. The claims reflect this manifest difference, by specifying that the nerve regeneration tube has an inner diameter of about 0.5-5mm.

The distinction between the presently claimed invention and the Geistlich et al. '109 patent further is made manifestly clear by the claims' recitation that the nerve regeneration tube is for reconnecting nerve ends, and further specifying that the nerve regeneration tube has opposite ends into which ends of nerves are inserted for reconnection and regeneration of the nerves.

As noted above, the Geistlich et al. '109 patent utilizes a collagen membrane to protect a patient's spine following vertebral surgery. There is no hint or even a remote suggestion in the Geistlich et al. '109 patent of a nerve regeneration tube for reconnecting nerve ends, the tube having opposite ends into which ends of nerves are inserted for reconnection and regeneration of the nerves, with the tube having an inner diameter of about 0.5-5mm. Accordingly, for at least the reasons presented above, the present claims are not rendered obvious by any combination of the cited art, particularly in light of the demonstration of unexpected results previously provided

and described herein. Therefore, Applicants respectfully request reconsideration and withdrawal of the above obviousness rejection.

Claims 2-3, 5-6, 9-11, 19, 14-17, 22-30 and 32-33 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Chamberlain, the '278 patent, and the '109 patent as applied to claims 2-3, 5-6, 9-11, 19, 14-16,22-30, and 32-33 above, and further in view of Fearnot et al. (US 6,358,284, "Fearnot"). The Office Action acknowledged that Chamberlain, the '278 patent, and the '109 patent do not teach a step of joining two opposite side edges of a collagen sheet material together to form a tube. According to the Office Action, Fearnot does teach a process for producing an implantable graft construct from a sheet of a highly purified form of an implantable tela submucosa collagen matrix (column 6, lines 45-65) formed in the shape of a tube having a seam extending longitudinally along the length of the graft wherein the seam has been sealed to resist movement of fluids from the lumen through the seam to the exterior of the tube (column 3, lines 32-38). The Office Action stated that the tubular prosthesis is envisioned for use with nervous tissue (column 2, lines 63-64). In the opinion expressed in the Office Action, it therefore would have been obvious to one of ordinary skill in the art at the time of the invention to make an implantable graft construct from a sheet of Bio-Gide® in the shape of a tube having a seam extending longitudinally along the length of the graft wherein the seam has been sealed to resist movement of fluids from the lumen through the seam to the exterior of the tube because of the desire to prevent wound-derived neurotrophic factors from leaking out, which the Office Action asserted is suggested by Chamberlain.

In response, Applicants respectfully traverse the rejection. Applicants first refer to the comments presented above in connection with the obviousness rejection based on Chamberlain, the '278 patent and the '109 patent. The further cited Fearnot reference does nothing to overcome the nonobviousness of the claims based on the unexpected results noted above, nor does it provide any other reason to suggest the claims are obvious over the presently cited art. For at least this reason, Applicants respectfully request reconsideration and withdrawal of the above obviousness rejection.

Claims 2-3, 5-7, 9-1 1, 19, 14-16, and 22-33 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Chamberlain, the '278 patent, and the '109 patent as applied to claims 2-3, 5-6, 9-1 1, 14-16, 19,22-30, and 32-33 above, and further in view of Humes (US 5,429,938, already of record).

The Office Action acknowledged that Chamberlain, the '278 patent, and the '109 patent do not teach a mixture of Type I and Type IV collagen in a ratio of about 1:1 for supporting biological activity. According to the Office Action, Humes does teach the use of Type I and Type IV collagen in about 1:1 ratios to support biological activity (column 3, lines 65-66). In the opinion expressed in the Office Action, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ Humes' ratio of about 1:1 of Type I and Type IV collagen because the other references do not quantitatively teach specific ratios between Type I and Type IV collagen for the desired aim of supporting biological activity. The Office Action asserted that Chamberlain provides additional motivation by teaching that collagen tubes have multiple advantages over silicone tubes, but that "the required characteristics of a nerve guide remain to be fully delineated" (page 1401). The Office Action further stated that while porous

collagen tubes permit diffusion of nutrients and growth-promoting factors from the external environment to the injured nerves in order to promote nerve regeneration (an observation the Office Action asserted is supported by two studies according to Chamberlain), if the tube is too porous, important wound-derived neurotrophic factors may be allowed to exit the injury site prematurely through the tube. The Office Action further stated that Chamberlain reports that his own study has shown that the most favorable results were obtained with a non-porous collagen tube filled with a CG copolymer because said tube facilitated the retention of the endogenous neurotrophic factors in the nerve injury gap site while allowing for the infiltration of smaller molecular weight nutrients through the tube. The Office Action stated that Chamberlain concludes "additional experimentation with porous and non-porous collagen tubes that differ in permeability may be used to address this issue" (page 1402), which, in the opinion expressed in the Office Action, is a suggestion by the primary reference to try to optimize the ratio of Type I and Type IV collagen for the known and motivating purpose of improving the therapeutic results. The Office Action thus concluded that the artisan would be motivated to look to the Humes reference to supply this missing information if said artisan was actually going to reduce to practice a combination of Type I and Type IV collagen because such information would be required during fabrication and use of the neural regeneration tube.

In response, Applicants respectfully traverse the rejection. Applicants first refer to the comments presented above in connection with the obviousness rejection based on Chamberlain, the '278 patent and the '109 patent. The further cited Humes reference does nothing to overcome the nonobviousness of the claims based on the unexpected results noted above, nor does it provide any other reason to suggest the claims are obvious over the presently cited art. Humes does not even relate to nerve regeneration tubes, but instead is directed toward a renal

tubule tissue system wherein adult kidney cells are cultured in a medium which may contain Type I collagen and/or Type IV collagen. Humes therefore cannot be combined with the other applied references to render obvious, or make predictable, the unexpected results achieved with the present invention. Therefore, for at least the reasons reiterated above, the invention is not obvious over the combination of reference teachings suggested in the Office Action.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the above obviousness rejection.

In view of the above remarks, and the claim amendment presented herein, Applicants believe all of the concerns set forth in the May 1, 2009 Office Action have been fully overcome and the application is in condition for allowance. The Examiner is invited to telephone the undersigned if it is deemed to expedite such allowance.

Respectfully submitted,

October 1, 2009 By _____

Patrick T. Skacel
Reg. No. 47,948
Attorney for Applicants
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
Suite 800, 1425 K Street, N.W.
Washington, D.C. 20005
Telephone: (202)783-6040

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